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Clinico-pathological conference

Metastatic cerebral lymphoma

L Hughes-Davies, M Spittle, M J Harrison, S B Lucas, R F Miller

Case report *(Dr L Hughes-Davies)*
The patient was a 42 year old artistic director who was well until 1982 when he presented with anal pruritis; this was managed conservatively. He then remained well until 1987 when he had a left lower lobe pneumonia associated with a small left pleural effusion. Investigations including bronchoscopy were negative and his symptoms and signs resolved spontaneously. Following this he requested an HIV test and was found to be HIV antibody positive. About this time he developed night sweats and began treatment with zidovudine at a dose of 1200 mg per day. In December 1987 he became anaemic, a bone marrow specimen showed erythroid aplasia, and the zidovudine was discontinued for 2 months. A repeat bone marrow examination off zidovudine in February 1988 was normal, and he restarted cyclical zidovudine therapy (four weeks on therapy and two weeks off). In August that year his CD4 count was 110/mm^3. In December 1988 he presented with a short history of breathlessness. A chest radiograph showed perihilar infiltrates, broncho-alveolar lavage was positive for *Pneumocystis carinii*. He received nebulised pentamidine and rapidly responded. The next 18 months were a good time for him and he had a good quality of life. In early 1990 he developed mid-thoracic back pain, and by May he had a fever, and had lost 10 kg in weight. A chest radiograph showed a left pleural mass (fig 1). Cytological examination of a fine-needle aspirate of the pleural mass revealed that this was a high-grade B cell non-Hodgkin's lymphoma. Staging investigations included a bone marrow aspirate and trephine which was negative, abdominal CT which showed only splenomegaly, but an ultrasound scan showed three hyperechoic areas in the liver which were thought to represent lymphomatous infiltrates. There was also 14 cm splenomegaly. We elected not to do a lumbar puncture. He was started on cyclical chemotherapy with Prednisolone, Adriamycin, Cyclophosphamide, Etoposide, Bleomycin, Methatrexate (PACE-BOM). This is a regime of combination chemotherapy; in the first week prednisolone is begun (and continued throughout the course) together with adriamycin, cyclophosphamide and etoposide, all of which are myelosuppressive. In the second week bleomycin, vincristine (=O) and methotrexate are given; this regime of alternating drugs is continued for 12–16 weeks. He received three 2 week cycles over 9 weeks; the course was delayed for a week half way through because of bone marrow suppression. During this treatment he had oral mucositis, total alopecia, recurrence of perianal herpes infection, and he also required a brief admission for blood transfusion. The patient felt he had a marked reduction in his quality of life and he resented being tied to the hospital to such an extent. In mid-July, half way

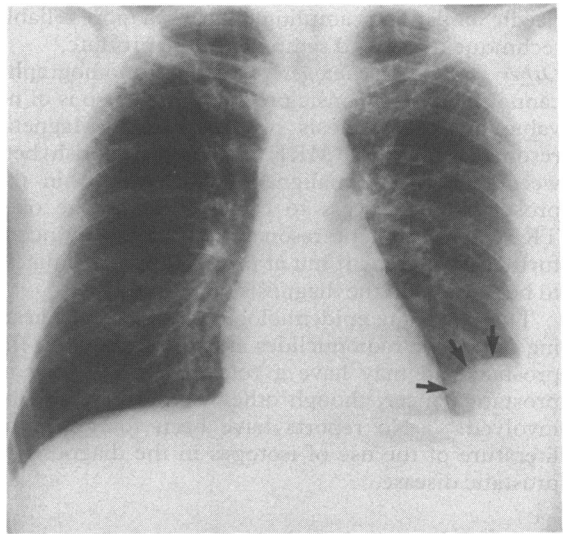

Figure 1 Chest radiograph showing a left pleural mass (arrows).

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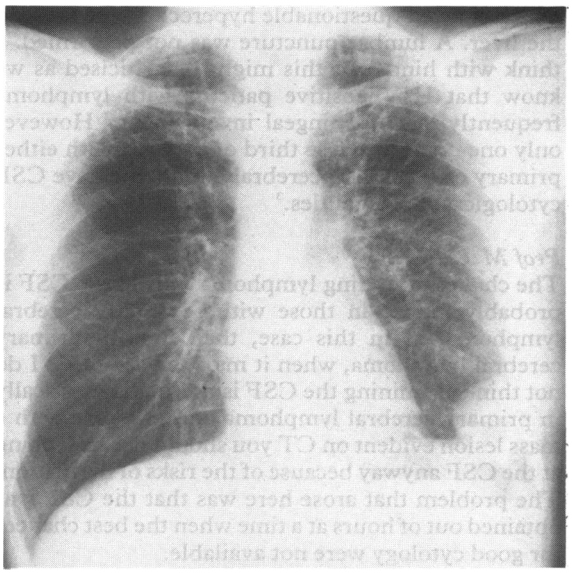


Figure 2 Chest radiograph, mid July, when restaging was carried out. There has been no change in size of the pleural mass and there is now interstitial shadowing in the lungs.

through the planned course of chemotherapy, he was restaged. A chest radiograph showed no evidence of tumour response and there was some increase in the interstitial lung shadowing (fig 2). Abdominal and pelvic CT scans were unremarkable, chest CT showed the pleurally based mass, together with interstitial shadows in both lungs. An open lung biopsy was planned; at the patient's request this was deferred. At that time he was very well and was keen to return to work. Shortly after this he became unwell. He appeared to be a little forgetful when seen in clinic—he had left his home to attend clinic without any money for his bus fare or his house keys. He was admitted acutely late one night a few days later. Both he and his partner reported that he had become dizzy, ataxic and intermittently incontinent of urine. On examination there were no focal neurological signs. He was apathetic and mentally slow, with lucid speech. He had a mild sensory peripheral neuropathy which was thought to be due to vincristine, and general examination was normal. Investigations showed Hb = 9·9 g/dl, WBC = 2·1 × 10^9/l; plasma sodium 132 (normal 137–145) mmol/l. Blood, urine and stool cultures were negative and the toxoplasma and CMV serology were negative. A lumbar puncture was performed that night. The opening pressure was 10·5 cm of water, and the CSF was clear. Analysis showed a protein of 0·41 g/l, there was a slightly high blood/CSF glucose gradient (blood glucose 6·3, CSF glucose 2·7 mmol/l) and there were no white cells. Cytological examination of the CSF was negative,

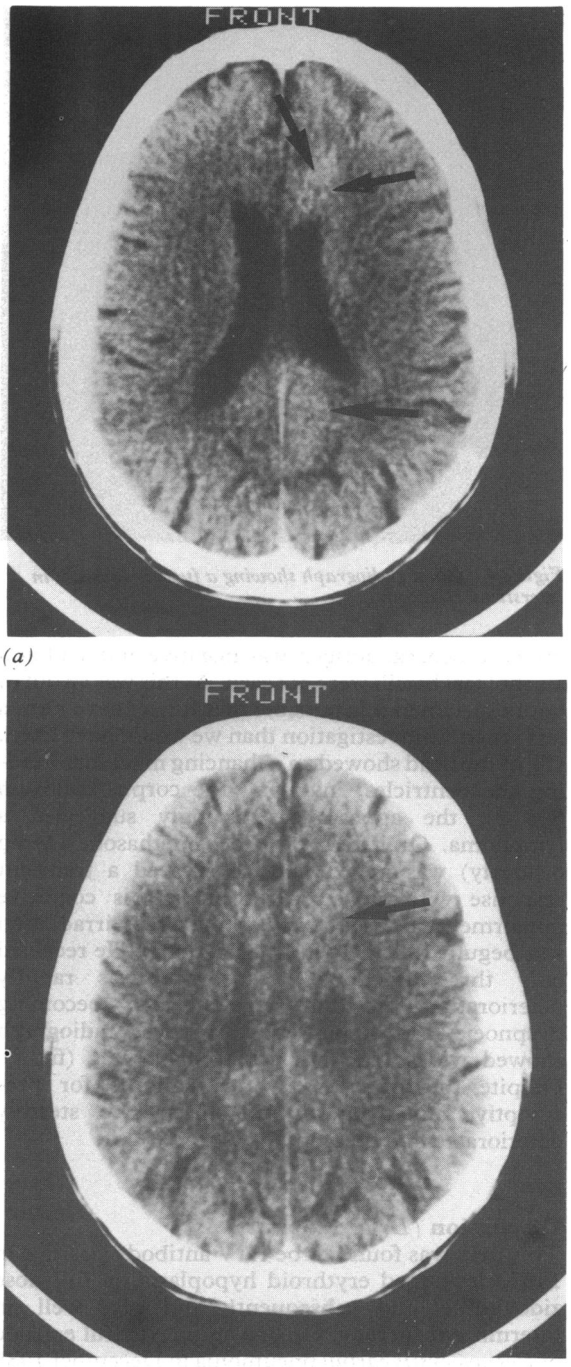


Figure 3 Contrast enhanced CT scan of the brain (a) at the level of the lateral ventricles. There is enchancement anteriorly in the body of the corpus callosum (arrows) and posteriorly in the splenium (arrow) (b) section above 3(a). There is extensive periventricular infiltration, this extends into the frontal lobe (arrow).

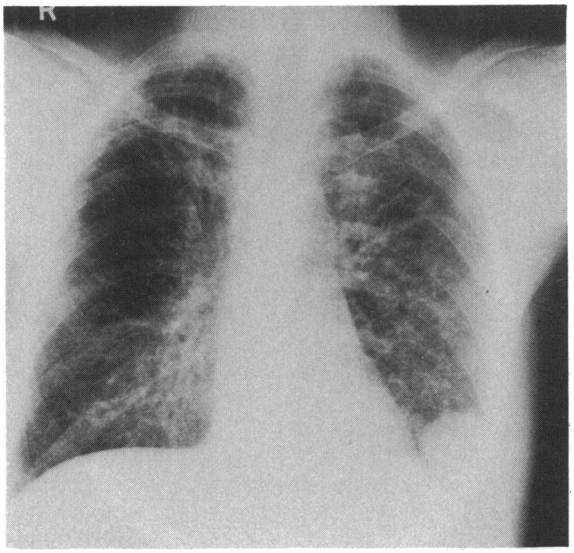


Figure 4 Chest radiograph showing a further increase in interstitial shadowing.

the cryptococcal antigen was negative and acid and alcohol fast bacilli were not seen. As this was an out of hours specimen it is possible that it may have been a less sensitive investigation than we would have liked. CT of the head showed an enhancing mass surrounding the ventricles, involving the corpus callosum (fig 3); the appearances strongly suggested a lymphoma. Oral high dose dexamethasone (4 mg 6-hourly) was begun and he showed a transient response with an improvement in his cognitive impairment. Subsequently whole brain irradiation was begun (1200 cGy in five fractions). He received only three fractions because he was rapidly deteriorating. At this stage he was becoming dyspnoeic and hypoxaemic, a chest radiograph showed widespread interstitial shadowing (fig 4). Despite therapy with IV pentamidine for presumptive pneumocystis pneumonia he steadily deteriorated and died.

Discussion *(Dr M F Spittle)*

This man was found to be HIV antibody positive in 1987, developed erythroid hypoplasia on full dose zidovudine[1] and subsequently did very well on intermittent therapy. He had an uneventful episode of *Pneumocystis carinii* pneumonia in December 1988 and was then well until presenting with weight loss, back pain and fever in May 1989. Fine needle aspiration of a left pleurally based mass revealed a non-Hodgkin's lymphoma and so he underwent staging investigations. These included a bone marrow aspirate and trephine, CT of the abdomen, which showed splenomegaly only, and an ultrasound which showed questionable hyperechogenic areas in the liver. A lumbar puncture was not performed. I think with hindsight this might be criticised as we know that HIV positive patients with lymphoma frequently have meningeal involvement.[2] However only one quarter to one third of patients with either primary or secondary cerebral lymphoma have CSF cytological abnormalities.[3]

Prof M J Harrison

The chance of finding lymphoma cells in the CSF is probably higher in those with secondary cerebral lymphoma, as in this case, than it is in primary cerebral lymphoma, when it may be very rare.[4] I do not think examining the CSF is useful diagnostically in primary cerebral lymphoma and in a case with a mass lesion evident on CT you should not be looking at the CSF anyway because of the risks of herniation. The problem that arose here was that the CSF was obtained out of hours at a time when the best chances for good cytology were not available.

Dr M F Spittle

That was certainly the situation on the second occasion when he presented with his cerebral symptoms but the question really is whether a lumbar puncture should have been done when he was first staged. So, this is an unusual presentation with lymphoma, he had "B" symptoms of fever and weight loss, and tumour at an extra nodal site. If the ultrasound diagnosis is discounted and the CT imaging relied on then this man had stage 1BE non-Hodgkin's lymphoma. This presentation is rarely seen outside the context of AIDS, but is very common in HIV positive patients.[5] He had chemotherapy with PACE-BOM which is thought to be the best treatment.[6] The chemotherapy in this patient was not a success story. The patient was very critical of the way the drugs had affected his quality of life and felt that he had not done well with the chemotherapy. This was unusual as most patients feel dramatically better from their first injection of chemotherapy for this sort of aggressive lymphoma. He had perianal herpes, total alopecia, and oral mucositis. Despite chemotherapy the pleural mass did not change in shape or size. It is unusual for an aggressive lymphoma not to show a response to therapy, they are usually extremely sensitive to chemotherapy. In view of this non response the patient was restaged in mid-July and an open lung biopsy was planned but deferred and then the patient was admitted in extremis and was found to have an abnormality by head CT. Despite the negative CSF cytology this was thought to be metastatic cerebral lymphoma and so whole brain irradiation was given.

Prof M J Harrison

I think the diagnosis of cerebral lymphoma was right.

It is not an easy diagnosis to make at the bedside. Something like two thirds of patients with cerebral lymphoma present with confusion, memory disturbance, and only about a third have the focal features to suggest the mass lesion that is really there, so the presentation is often initially confused with the non-specific effects of hypoxia and co-existing chest infection or other metabolic problems.[7] Presumably the incontinence was in fact the focal feature in this man because he had a frontal mass; that is an accepted feature of frontal pathology. The CT diagnosis is difficult because ultimately you may not be able to distinguish toxoplasma abscess, for example, from a lymphoma. Although the tumours are commonly multiple at autopsy, at the stage at which you are looking at the patient clinically multiple lesions are more likely to be abscesses and a solitary lesion is much more likely to be a lymphoma. Apart from that you cannot make the ultimate distinction. You may see in a lymphoma, the same mass effect, and even the ring-enhancement that you expect to see in toxoplasmosis.[8 9] There is often a need for biopsy when there isn't a systemic tumour to support the imaging diagnosis.

Dr M F Spittle
How readily can you rely on the negative toxoplasma serology and was CT the appropriate investigation to have done?

Prof M J Harrison
The toxoplasma serology is not that helpful, as negative serology does not exclude cerebral toxoplasmosis.[10] MRI is more sensitive than CT, but it does not tell you exactly what you are looking at. In fact it is not as good as CT at giving an indication of the pathology, but it does show you if there are multiple lesions when sometimes the CT only sees one. That is valuable in two ways. If you saw multiple lesions, it would be more likely to be toxoplasma than lymphoma. So if the lesion is genuinely solitary even on MRI, up goes the confidence with which you suspect lymphoma. The second thing is that you may see a lesion that can be more readily and safely biopsied than the one that you see on CT.

Dr R F Miller
Should we have performed a brain biopsy?

Prof M F Harrison
He failed to respond to chemotherapy. He was having radiotherapy. The lack of a biopsy did not hold up giving him radiotherapy so I suspect that it would not have changed the outcome. There are many other situations, however, when I think that an early biopsy is indicated, particularly when you are seeing failure of anti-toxoplasma treatment in an otherwise well patient with a focal cerebral lesion of uncertain nature.[11] In this case there was less diagnostic difficulty because he had a systemic lymphoma.

Dr M F Spittle
We usually see radiotherapeutic resistance mirrored by chemotherapeutic resistance in most tumours and the remarkable feature was the chemoresistance in the lung. This is in contradistinction to primary cerebral lymphomas to which these patients are prone where it appears that if you can give a reasonable dose of radiotherapy and the patient's quality of life is sufficiently good to justify it those patients then do not go on to die of lymphoma.[7] So it does seem in the series reported to be worthwhile to give radiation as soon as one can make the diagnosis. If one treats aggressively in this way, the lymphoma does respond and the patients have some improvement in quality of life. It is interesting that the lymphomas seem to occur in patients who have a CD4 count below 100 per mm^3.[12]

Prof M J Harrison
This is an important point. The conventional view of the prognosis has been that patients only survive 2 to 3 months after the diagnosis of primary cerebral lymphoma. This has rather put people off attempting aggressive treatment. In fact the poor prognosis reflects the severity of immunosuppression, rather than the effects of the lymphoma. Primary lymphoma occurs late in the patient's course. Do you think that this was a metastatic tumour in the brain?

Dr M F Spittle
Yes. With non-Hodgkin's lymphoma one does not usually see the standard metastatic progression that one does in Hodgkin's disease but this is metastatic and certainly not primary cerebral lymphoma. In AIDS patients unusual presentations are not infrequently seen; these include primary cardiac lymphoma and rectal lymphoma which are unusual in a non-AIDS setting.[2 13] Although the bone marrow is frequently positive in these patients, as you would expect in these aggressive non-Hodgkin's lymphomas, the brain seems to be one of the protected sites where disease persists. This demonstrates that our chemotherapy agents do not cross the blood brain barrier well. In patients who are fit it is a reasonable suggestion to give CNS prophylaxis. Regular intrathecal chemotherapy, either methotrexate or cyclizine arabinoside is fairly invasive for the patient. It is given when the patient is otherwise fit and there is no obvious CNS involvement.

Clinical diagnoses:
1 Cerebral and pulmonary lymphoma
2 *Pneumocystis carinii* pneumonia

Dr S Lucas
One thing I have learned from our series of over

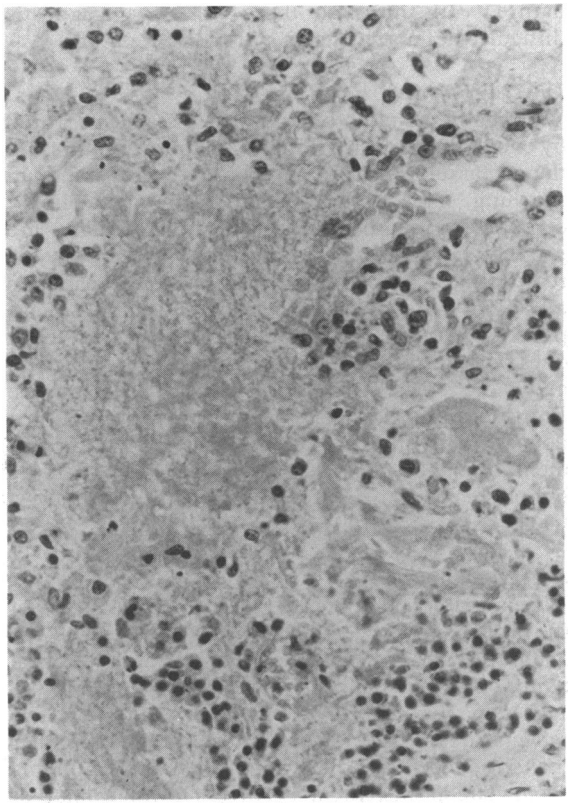


Figure 5 Left lower lobe pleurally based tumour (× 400 magnification) showing that it is composed of Pneumocystis carinii intermingled with lymphoma cells (H & E).

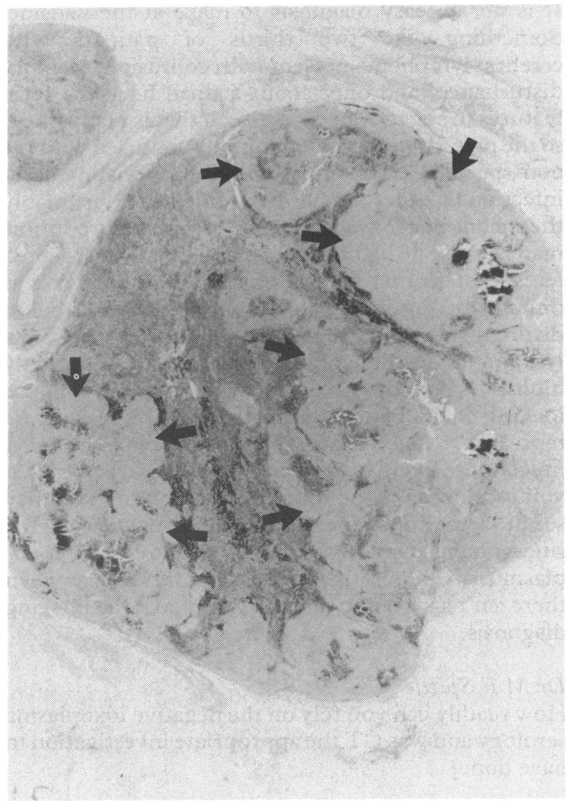


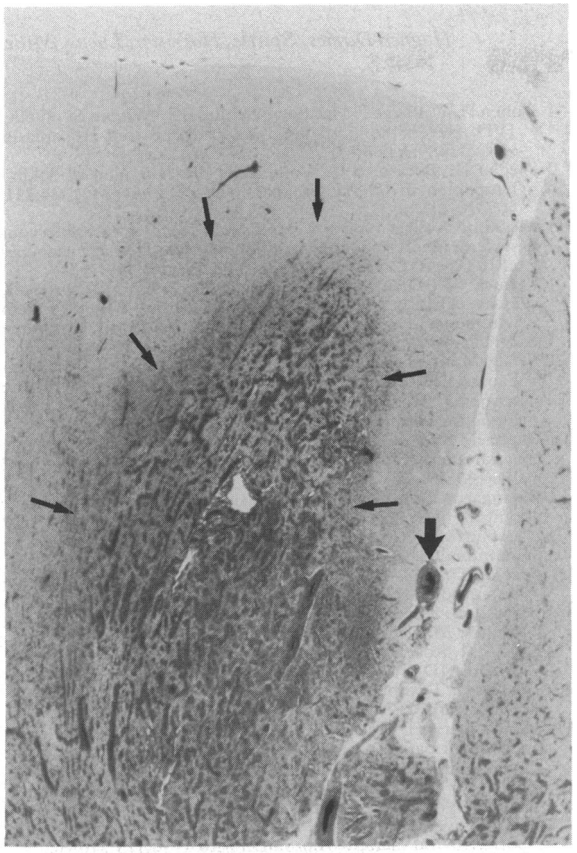
Figure 6 Hilar lymph node (× 10 magnification) showing that the normal architecture is partially replaced by pale amorphous material (arrows) which is Pneumocystis carinii. No lymphoma is seen (H & E).

40 AIDS autopsies is that experience from other autopsies has not really prepared me for what I see in these cases—with such bizarre presentations of lesions we have rarely seen before in the general population. Virtually everything I saw macroscopically at autopsy in this man I guessed incorrectly. Your clinical diagnosis is fairly right.

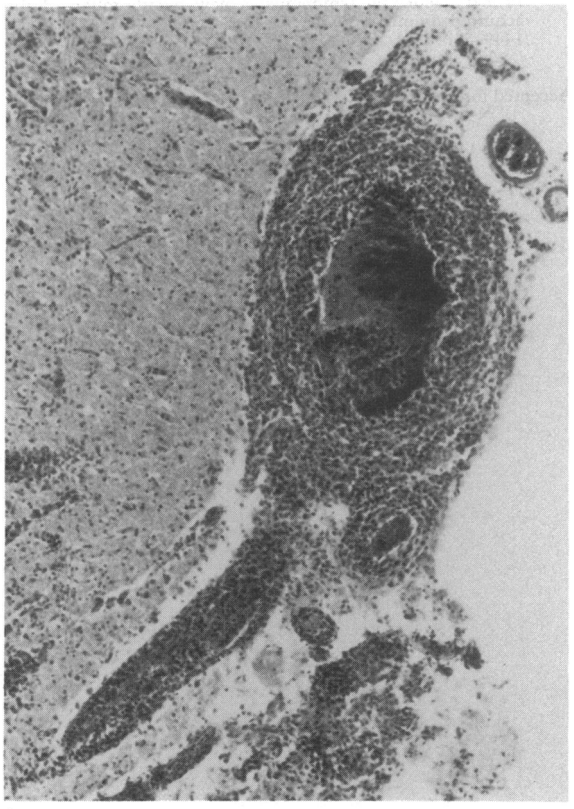
This was a thin man, bald because of his chemotherapy. The heart and major blood vessels were normal. In the lungs there was a little pleural adhesion in the left lower lobe; the lungs were both moderately heavy weighing 700 g each (the right lung normally weighs 620 g and the left lung 560 g) and there were widespread, small yellowish necrotic lesions. There was a 4 cm diameter necrotic, white tumour at the left costophrenic angle which was invading the diaphragm. I thought that this was the lymphoma which we know about and that the remaining lung was going to show non-specific sepsis, because I also thought there was some bronchiectasis. There were small cavities as well, connecting with the bronchi. I thought that this man had died of staphylococcal pneumonia on top of his lymphoma.

The tongue appeared abnormal, with what turned out to be oral hairy leucoplakia; the rest of the gastrointestinal tract including the liver was entirely normal. The spleen was of normal size and showed no lymphoma. The hilar nodes had pale yellow nodules in them which were suspicious of *Pneumocystis carinii* infection. Elsewhere around the body the other nodes were normal for a patient with end-stage AIDS—they were atrophic. The adrenals were small, because of the steroid therapy he had received, with lots of small red haemorrhages, suggesting cytomegalovirus infection.

The brain was fixed for 4 weeks then examined. Our success rate at guessing the eventual histopathological diagnosis on the basis of the macroscopic appearances at autopsy is often no better than 50%; we confuse the appearances of cerebral lymphoma with cytomegalovirus infection and toxoplasmosis. In this patient the brain was externally normal, of normal weight (1360g) and was not swollen. On section there was a slight granular abnormality apparent along the lateral ventricles anteriorly, along the cortex and the falx, and that was all. I wondered whether these appearances could be due to toxoplasmosis, lymphoma or even HIV-



(a)



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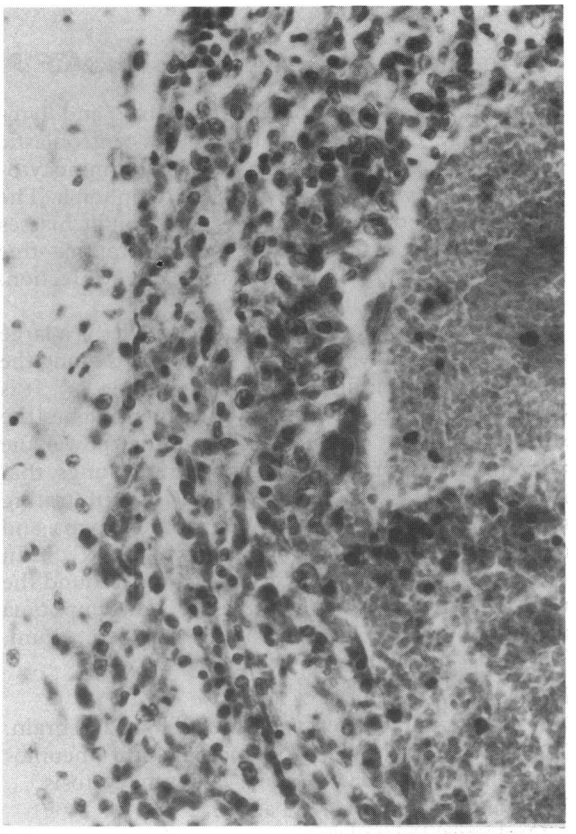

(c)

Figure 7 (a) Cerebral cortex from region adjacent to falx (× 10 magnification) showing infiltrating lymphoma (arrows). The small artery (short arrow) is filled with lymphoma (H & E). (b) Higher power (× 100 magnification) of the small artery seen in (a); it is filled with lymphoma cells (H & E). (c) At high magnification (× 400) the lymphoma cells are seen to be infiltrating through the wall of the artery (H & E).

induced encephalitis. The spinal cord and peripheral nerves were normal.

Histologically this patient was colonized by cytomegalovirus. In the bowel there was one tiny area in the ileum of cytomegalovirus vasculitis in blood vessels in the submucosa. The liver contained focal small abscesses, many of which contained cytomegalovirus inclusions. In the adrenals, the haemorrhagic foci seen macroscopically were due to cytomegalovirus adrenaitis with vascular obstruction. These appearances rarely cause any clinical disease, as was the case with this patient, who had no evidence of adrenal insufficiency prior to death. The lungs contained multiple nodules and also cavities. There is focal pyogenic acute bronchitis and widespread *Pneumocystis carinii* infection. This was what the yellowish nodules were that were seen macroscopically. In addition there is cytomegalovirus in the lungs, but I do not think it is causing any problems as it is not associated with active necrosis.

The pulmonary tumour is necrotic lymphoma and there is *Pneumocystis carinii* intermingled with it.

This is a combined "pneumocystoma" and lymphoma (fig 5). The lymphoma appears centroblastic with some smaller centrocytic cells. Immunocytochemistry showed this to be a B cell lymphoma. The hilar lymph node (fig 6) contains eosinophilic masses filling the tissue; there is also some calcification—this is extrapulmonary *Pneumocystis carinii* infection. There is no lymphoma in the lymph node.

In the brain around the lateral ventricles is a large mass of invading lymphoma. In the cortex along the falx there is also infiltrating lymphoma (fig 7a). It is involving the deep meninges, but never reaches the surface meninges of the brain. At higher power the lymphoma cells are similar to those in the lungs, that is, centroblastic. The lymphoma is infiltrating through vessel walls in the brain parenchyma and meninges so it is angioinvasive (figs 7b & c). In addition to lymphoma along the falx and around the ventricles there were other small foci of lymphoma throughout the brain, including the cerebellum. There was no lymphoma in the spinal cord.

Pathological diagnoses:

1 B cell lymphoma (centroblastic) of lung and brain.
2 *Pneumocystis carinii* pneumonia with pneumocystoma and extra pulmonary pneumocystosis.
3 Cytomegalovirus colonization.
4 Oral hairy leucoplakia.

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